DEPARTMENT OF HEALTH & HUMAN SERVICES

HFA-305

Food and Drug Administration
Rockville MD 20857

JUL 23 1999

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John A. Sweep, Esq.
Director
Direct Pharmaceuticals Ltd.
222 Merchant Street
Valletta, Malta VLT10

Docket No. 82N-0165
Comment No. CP3

Dear Mr. Sweep:

This is in response to your company's citizen petition dated July 24, 1995. The petition was filed as CP3 under Docket No. 82N-0165 in FDA's Dockets Management Branch. The petition requested the following: (1) the transfer of the active ingredient, Cimicifuga racemosa, from the Center for Drug Evaluation and Research (CDER) to the Center for Food Safety and Applied Nutrition (CFSAN) as a dietary supplement for use in normal estrogen deficiency under the provisions of the Dietary Supplement Health and Education Act (DSHEA) of 1994, (2) accept and review the data submitted for the company's trade name product "Remifemin Tablets" containing Cimicifuga racemosa, (3) delete the active ingredient, Cimicifuga racemosa (black cohosh), from the tentative final monograph (TFM) for OTC (over-the-counter) orally administered menstrual drug products (53 FR 46194 at 46198), and (4) delete Cimicifuga racemosa from 21 CFR 310.545(a)(24). The submission included labeling and stability information, 6-month animal oral toxicity data, and literature references of clinical trials.

The Office of Drug Evaluation V, CDER and the Office of Special Nutritionals, CFSAN have reviewed your petition and determined the following:

1) Your request to transfer the review and consideration of Cimicifuga racemosa from CDER to CFSAN for inclusion in the appropriate dietary supplement rulemaking under the provisions of DSHEA is denied. CFSAN currently has no dietary supplement rulemakings under the provisions of DSHEA to address specific claims for specific products. Therefore, there is no appropriate dietary supplement rulemaking applicable to Cimicifuga racemosa.

2) Your request to accept and review data submitted for your company's product "Remifemin," a dietary supplement containing Cimicifuga racemosa, is denied. There is no requirement for the agency to review data or other information prior to a manufacturer marketing a substance that meets the definition of a dietary ingredient as defined in section 201(ff) of the Federal Food, Drug and Cosmetic Act (the act), as amended by DSHEA of 1994. Furthermore, although the act does require that a manufacturer who proposes to make a claim on the label or in the labeling of a dietary

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supplement under section 403(r)(6) of the act have substantiation that the claim is truthful and not misleading, the act does not require a manufacturer to submit such substantiation to the agency. A manufacturer making a claim under section 403(r)(6) of the act in the label or labeling of a dietary supplement must notify FDA that the claim is being made no later than 30 days after the first marketing of the dietary supplement with the statement. In addition, the label and labeling may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases. It must also contain a disclaimer specified by section 403(r)(6) of the act.

3) Your request to delete Cimicifuga racemosa (black cohosh) from the list of menstrual active ingredients in the proposed rulemaking for OTC orally administered menstrual drug products published in the FEDERAL REGISTER of November 16, 1988 (53 FR 46194 at 46198) is denied. Cimicifuga racemosa was reviewed by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel) as part of its review of all OTC orally administered menstrual drug products. The Panel classified Cimicifuga racemosa as Category II (not generally recognized as safe and effective) for use as an OTC drug in relieving the symptoms of premenstrual syndrome and primary dysmenorrhea. This finding was published in the advance notice of proposed rulemaking for OTC orally administered menstrual drug products in the FEDERAL REGISTER of December 7, 1982 (47 FR 55076).

In its evaluation, the Panel indicated that, while Cimicifuga racemosa has a history of use in folk medicine, there are no substantive data that the ingredient was generally recognized as safe and effective for use as an orally administered OTC menstrual drug product to treat the symptoms related to women's menstrual cycles. The Panel also noted that, although a 150 year history of use of Cimicifuga racemosa fluid extract at levels of up to 890 mg a day gives some reassurance of the safety of this compound, additional safety testing is needed, particularly in light of reported toxic effects of the compound on the respiratory and circulatory system (47 FR 55092). The Panel also noted that no long-term human or animal studies on the safety of Cimicifuga racemosa were submitted. Because no substantive data supporting the safety and effectiveness of Cimicifuga racemosa were submitted, the agency concurred with the Panel's Category II classification for Cimicifuga racemosa in the tentative final monograph for OTC orally administered menstrual drug products published in the FEDERAL REGISTER on November 16, 1988 (53 FR 46194). Therefore, Cimicifuga racemosa was properly and correctly regarded and listed as an active ingredient in this FEDERAL REGISTER publication and no evidence or argument disputing the classification was provided in your petition.

4) Your request to delete Cimicifuga racemosa from 21 CFR 310.545(a)(24) is also denied. In the FEDERAL REGISTER of May 10, 1993 (58 FR 27636), codified under 21 CFR 310.545, the agency published a final rule removing from the market all Category II and III active ingredients for which no new substantive safety and/or effectiveness data and no substantive comments in opposition to the agency's proposed nonmonograph status for these ingredients had been submitted. Any active ingredient

that is listed in this regulation may not be marketed for the use or indication listed in the regulation without an approved application or abbreviated application under section 505 of the act and 21 CFR part 314 of the regulations or an amendment or promulgation of an OTC drug monograph containing that ingredient.

Cimicifuga racemosa as an OTC orally administered menstrual drug was included in the above agency regulation in §310.545(a)(24). Accordingly, any product containing Cimicifuga racemosa as an active ingredient with labeling claims as an orally administered product for use in treating the symptoms of women's menstrual cycles is considered a drug and shall remain subject to the regulations in §310.545(a)(24). No data or evidence was provided by your petition to dispute this classification.

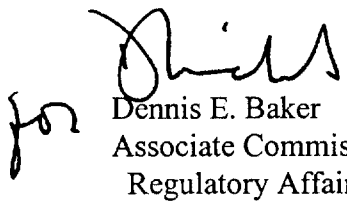
For the foregoing reasons, your request to delete the active ingredient, Cimicifuga racemosa, from the TFM for OTC orally administered menstrual drug products and from 21 CFR 310.545(a)(24) and your request to transfer Cimicifuga racemosa from CDER to CFSAN for inclusion in the appropriate dietary supplement rulemaking under the provisions of DSHEA of 1994 are denied.

Should you have further questions regarding the status of Cimicifuga racemosa as a dietary supplement under the provisions of DSHEA or on the dietary supplement regulatory process under DSHEA, we recommend that you contact the Division of Programs and Enforcement Policy, Office of Special Nutritionals, CFSAN, 202-205-5372.

If you have any questions regarding this matter, please refer to the docket and comment numbers noted above and submit all inquiries in triplicate to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, Maryland 20852.

We hope this information will be helpful.

Sincerely yours,



for Dennis E. Baker
Associate Commissioner for
Regulatory Affairs

cc: Miriam P. Calhoun
Consultant to Australian Bodycare Corp.
13310 River Road
Potomac, Maryland 20854

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUL 23 1999

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 82N-0165

TO: Dockets Management Branch, HFA-305

[X] The attached material should be placed on public display under the above referenced Docket No.

[X] This material should be cross-referenced to Comment No. CP3

Charles J. Ganley, M.D.

Attachment